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(54) **COMBINATIONS OF DOLUTEGRAVIR AND LAMIVUDINE FOR THE TREATMENT OF HIV INFECTION**

ZUSAMMENSETZUNGEN AUS DOLUTEGRAVIR UND LAMIVUDIN ZUR BEHANDLUNG VON DURCH HIV VERURSACHTEN INFEKTIONEN

COMBINAISONS DU DOLUTÉGRAVIR ET DE LA LAMIVUDINE DESTINÉES AU TRAITEMENT DE L'INFECTION AU VIH

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Description**BACKGROUND OF THE INVENTION**

[0001] The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of CD4⁺ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

[0002] In addition to CD4, HIV requires a co-receptor for entry into target cells. The chemokine receptors function together with CD4 as co-receptors for HIV. The chemokine receptors CXCR4 and CCR5 have been identified as the main co-receptors for HIV-1. CCR5 acts as a major co-receptor for fusion and entry of macrophage-tropic HIV into host cells. These chemokine receptors are thought to play an essential role in the establishment and dissemination of an HIV infection. Therefore, CCR5 antagonists are thought to be useful as therapeutic agents active against HIV.

[0003] As in the case of several other retroviruses, HIV encodes the production of a protease which carries out post-translational cleavage of precursor polypeptides in a process necessary for the formation of infectious virions. These gene products include pol, which encodes the virion RNA-dependent DNA polymerase (reverse transcriptase), an endonuclease, HIV protease, and gag, which encodes the core-proteins of the virion.

[0004] One focus of anti-viral drug design has been to create compounds which inhibit the formation of infectious virions by interfering with the processing of viral polyprotein precursors. Processing of these precursor proteins requires the action of virus-encoded proteases which are essential for replication. The anti-viral potential of HIV protease inhibition has been demonstrated using peptidyl inhibitors.

[0005] A required step in HIV replication in human T-cells is the insertion by virally-encoded integrase of proviral DNA into the host cell genome. Integration is believed to be mediated by integrase in a process involving assembly of a stable nucleoprotein complex with viral DNA sequences, cleavage of two nucleotides from the 3' termini of the linear proviral DNA and covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The repair synthesis of the resultant gap may be accomplished by cellular enzymes. Inhibitors of HIV integrase can be effective in treating AIDS and inhibiting viral replication.

[0006] Administration of combinations of therapeutic compounds in the treatment of HIV infection and related conditions can result in potentiated antiviral activity, reduced toxicity, delayed progression to resistance, and increased drug efficacy. Combinations administered in a single dosage unit can result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified. However, not all compounds are suitable for administration in combinations. Factors that influence the feasibility of combinations include the chemical instability of the compounds, size of the dosage unit, potential for antagonistic or merely additive activities of the combined compounds, and difficulties in achieving a suitable formulation.

[0007] NCT 0951015 (<http://clinicaltrials.gov/ct2/show/NCT00951015>) is a Phase IIb clinical trial into the use of do-lutegravir (GSK1349572) in the treatment of HIV-1.

[0008] Exp. Opin. Drug Metab. Toxicol. 2010, 6(1), 105 discusses lamivudine for the treatment of HIV.

[0009] There is continued need to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to treat HIV infection. Due to their high potency and pharmacokinetic profile, certain HIV integrase inhibitors are attractive as components in combination therapy.

BRIEF DESCRIPTION OF THE FIGURES**[0010]**

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).

Figure 2: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with efavirenz (EFV).

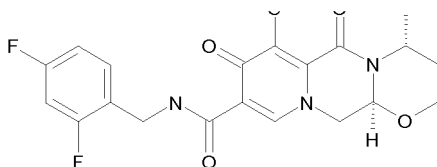
Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)

SUMMARY OF THE INVENTION

[0011] The present invention relates to combinations and pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and lamivudine. Such combinations are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention relates to combinations comprising a compound of the following formula (I):



or a pharmaceutically acceptable salt thereof, and lamivudine.

[0013] The present invention relates to such combinations for use in methods of treatment of HIV infection, AIDS, and AIDS related conditions.

[0014] The compound of formula (I) is also known as GSK1349572. A chemical name of the compound of formula (I) is (4R, 12aS)-N-[2,4-fluorophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-2H-pyrido [1',2':4,5]pyrazino [2,1-b] [1,3] oxazine-9-carboxamide.

[0015] The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

[0016] The term "treatment" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. Treatment may include prophylaxis which refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

[0017] As used herein, the term "subject" refers to a patient, animal or a biological sample.

[0018] Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. An advantageous salt is sodium salt.

[0019] Salts of the compounds of the present invention may be made by methods known to a person skilled in the art. For example, treatment of a compound of the present invention with an appropriate base or acid in an appropriate solvent can yield the corresponding salt.

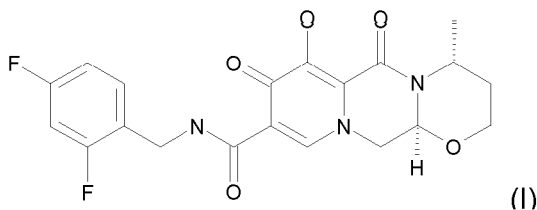
[0020] The present invention relates to combinations of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and lamivudine for use in methods of treating or preventing viral infection, for example an HIV infection, in a human.

[0021] The combination may be administered simultaneously or sequentially.

[0022] The combination is particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment may extend to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

[0023] The compound of formula (I), or a pharmaceutically acceptable salt thereof, and lamivudine administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[0024] The present invention features a combination comprising a compound of formula (I)



or a pharmaceutically acceptable salt thereof, and lamivudine.

[0025] The present invention features a compound of formula (I), or a pharmaceutically acceptable salt thereof, and lamivudine for use in medical therapy.

[0026] The present invention also features a compound of formula (I), or a pharmaceutically acceptable salt thereof, and lamivudine for use in the treatment of HIV infection.

[0027] The present invention features a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and lamivudine.

[0028] The present invention features combinations, pharmaceutical compositions and their uses as described above wherein a pharmaceutically acceptable salt of a compound of formula (I) is a sodium salt.

[0029] The present invention features combinations and pharmaceutical compositions for use as described above wherein the subject is a human.

[0030] The present invention features combinations and pharmaceutical compositions for use as described above wherein the combination is administered sequentially.

[0031] The present invention features combinations and pharmaceutical compositions for use as described above wherein the combination is administered simultaneously or concurrently.

[0032] Compounds of formula (I) may be made by methods disclosed in WO 2006/116764, U.S. 61/193,634 (WO2010/068253) or 61/193,636 (WO2010/068262).

[0033] Lamivudine may be made by methods disclosed in U.S. Patent Nos. 5,047,407; 7,119,202; 5,905,082; 5,696,254; 5,663,320; 5,693,787; 6,051,709; or 6,329,522.

[0034] The therapeutic agents of the combinations may be made according to published methods or by any method known to those skilled in the art.

[0035] In an aspect of the invention, a compound of formula (I), or a pharmaceutically acceptable salt thereof may be formulated into compositions together with lamivudine.

[0036] The composition may be pharmaceutical composition, which comprises a compound of formula (I), lamivudine, and a pharmaceutically acceptable carrier, adjuvant or vehicle. In one embodiment, the composition comprises an amount of a combination of the present invention effective to treat or prevent viral infection, for example an HIV infection, in a biological sample or in a patient. In another embodiment, combinations of the invention and pharmaceutical compositions thereof, comprising an amount of a combination of the present invention effective to inhibit viral replication or to treat or prevent a viral infection or disease or disorder, for example an HIV infection, and a pharmaceutically acceptable carrier, adjuvant or vehicle, may be formulated for administration to a patient, for example, for oral administration.

[0037] The present invention features combinations according to the invention for use in medical therapy, for example for the treatment or prophylaxis of a viral infection, for example an HIV infection and associated conditions. The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraparesis, anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

[0038] The present invention further includes the use of a combination according to the invention in the manufacture of a medicament for simultaneous (concurrent) or sequential administration to a subject for the treatment of a viral infection, in particular and HIV infection.

[0039] The combinations of the present invention may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present invention features a method for the treatment or prophylaxis of a disease as hereinbefore described by administration of a compound of the present invention in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

[0040] In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, in the range of 0.1 to 100 mg per kilogram body weight per day; in the range 1 to 30 mg per kilogram body weight per day; in the range 0.5 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredients are calculated as the parent compound of formula (I), and lamivudine.

[0041] For salts thereof, the weights would be increased proportionally. The desired dose may be presented as one,

two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 2000 mg; 5 to 500 mg; 10 to 400 mg, 20 to 300 mg of each active ingredient per unit dosage form.

[0042] The combinations may be administered to achieve peak plasma concentrations of each active ingredient.

[0043] While it is possible for the active ingredients to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present invention comprise an active ingredient, as defined above, together with one or more acceptable carriers thereof and one or more additional therapeutic agents. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

[0044] Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

[0045] The present invention further includes a pharmaceutical composition as hereinbefore defined wherein a compound of the present invention or a pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

[0046] Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3(6), 318 (1986).

[0047] Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0048] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

[0049] Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0050] Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray. Pharmaceutical compositions may contain in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0051] Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

[0052] Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0053] Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

[0054] Pharmaceutical compositions of the present invention may be presented as patient packs containing one or more courses of treatment in a single package, for example, a blister pack. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each composition, is an additional feature of the invention.

[0055] It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this invention may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

Examples

Example 1: Biological Activity

Assays

Method

[0056] Antiviral HIV activity was measured by means of a tetrazolium-based colorimetric procedure in the human T-cell leukemia virus (HTLV-1) transformed cell line MT-4. Aliquots of test compound were diluted vertically across a deep-well master assay plate, in medium (RPMI 1640, 10% vol./vol. fetal bovine serum (FBS), and 10 µg/mL gentamicin), at concentrations that were approximately 40-fold higher than the final assay concentration. Serial dilutions were made at either 1:2 or 1:3.16 ratios. HIV inhibitors were diluted horizontally across master assay plates, also in concentrations that were approximately 40-fold higher than the final assay concentration. Small aliquots of both the vertically-diluted and the horizontally-diluted compounds were combined in daughter plates using an automated 96-well pipetting system (RapidPlate-96, Zymark Corp.). Checkerboard style dilutions were arranged so that every concentration of test compound was tested in the presence and absence of every concentration of the HIV inhibitors. Anti-HIV activity tests were performed in triplicate assays, or more, of each combination. Exponentially growing MT-4 cells were harvested and centrifuged at 1,000 rpm for 10 minutes in a Jouan centrifuge (Model CR 4 12). Cell pellets were re-suspended in fresh medium (RPMI 1640, 20% vol./vol. FBS, 20% vol./vol. IL-2, and 10 µg/mL gentamicin) to a density of 1.25×10^6 cells/mL. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection (MOI) of 73 pfU per 1×10^4 cells. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hour at 37°C in a tissue culture incubator with humidified 5% CO₂ atmosphere. After the 1 hour incubation the virus/cell suspension was added to each well of the plates containing pre-diluted compounds. Plates were then placed in a tissue culture incubator with humidified 5% CO₂ for 5 days. At the end of the incubation period, 40 µL of CellTiter 96 MTS reagent (Promega no. G3581) was added to each well of the incubation plate. Plates were incubated at 37°C for 2 to 3 hours to allow for color development. O.D. was measured at 492 nm using a microplate absorbance reader (Tecan no. 20-300).

Virus used

[0057] HIV-1 strain IIIB, wild-type laboratory strain, virus titer = 6.896 E4 TCID₅₀/mL.

Data Analysis

[0058] Although some assay formats might theoretically miss antagonism due to combination cytotoxicity, the approach described here should not miss an antagonistic effect. The readout in the MT-4 cell assay utilizes MTS, a tetrazolium-based staining reagent where changes in optical density (O.D.) of the reagent are used to estimate the total cell number remaining after treatment. Final MT-4 cell numbers may decrease due to two effects. First, an HIV-induced cytotoxicity may occur when HIV kills greater than 75% of the MT-4 cells during the 5 days following infection. Second, a compound-induced cytotoxicity may occur, where the compound either directly kills the MT-4 cells or prevents cell growth (stasis) over the 5 days in either infected or uninfected cells. In either of these situations the O.D. is low as compared with infected cells protected by anti-HIV-1 compounds or relative to untreated and uninfected control cells. Since both cytotoxic effects and antagonism of anti-HIV activity would lead to lower O.D. we should not miss an antagonistic effect due to combination cytotoxicity, but could underestimate synergistic combinations.

[0059] Within assay combination cytotoxicity was evaluated by comparing wells containing the uninfected MT-4 cells from the assay plates that contained the highest concentration of test compound or the comparator compound, with

wells containing HIV-1 infected MT-4 cells under the corresponding highest combination concentrations. For each of these values there is one well per assay plate and thus at least 3 wells per combination assay. Although they do not comprise a formal combination cytotoxicity analysis, the ratio of compound in combinations to compound alone provides a measure of the compound combination cytotoxicity within the concentrations examined.

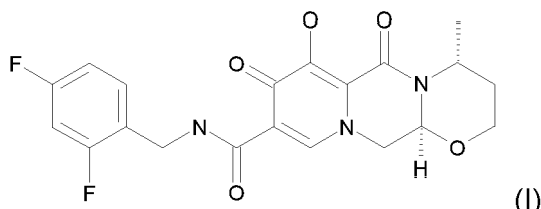
[0060] The interaction of each pair of compound combinations was analyzed by the methods described by Selleseth, D.W. et al. (2003) *Antimicrobial Agents and Chemotherapy* 47:1468-71. Synergy and antagonism are defined as deviations from dosewise additivity, which results when two drugs interact as if they were the same drug. Values for average deviation from additivity in the range of - 0.1 to - 0.2 indicate weak synergy and values that approach - 0.5 would indicate strong synergy of the interaction. Conversely, positive values of 0.1 to 0.2 would indicate that a weak antagonism exists between the treatments.

Results (reference)

[0061] A compound of formula (I) was found to be additive with raltegravir, adefovir, and maraviroc and was not affected by the presence of ribavirin. A compound of formula (I) was found to be synergistic with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide.

Claims

1. A combination comprising a compound of formula (I)



or a pharmaceutically acceptable salt thereof, and lamivudine.

2. A combination according to 1 wherein the pharmaceutically acceptable salt of a compound of formula (I) is the sodium salt.

3. A combination according to claim 1 for use in medical therapy.

4. A combination according to claim 1 for use in the treatment of HIV infection.

5. A pharmaceutical composition comprising a combination according to claim 1 together with a pharmaceutically acceptable carrier therefor.

6. A combination for use according to claim 4 wherein the combination is administered simultaneously.

7. A combination for use according to claim 4 wherein the combination is administered sequentially.

8. Use of a combination according to claim 1 for the manufacture of a medicament for the treatment of HIV infection.

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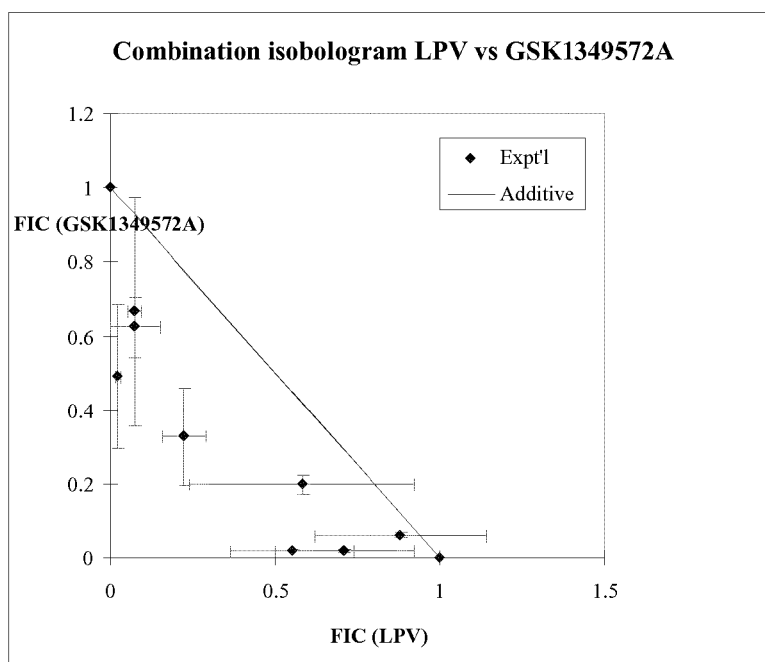


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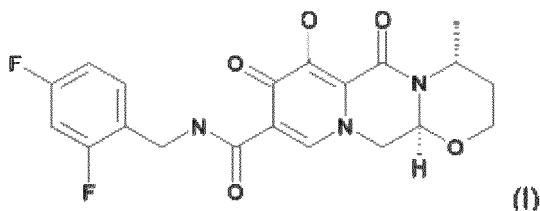
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Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)



Patentansprüche

1. Kombination, umfassend eine Verbindung mit der Formel (I)



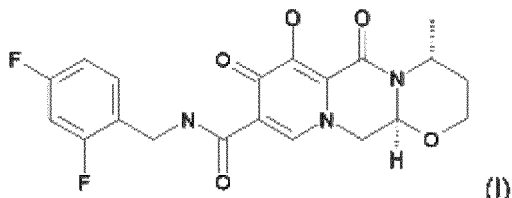
oder ein pharmazeutisch annehmbares Salz hiervon und Lamivudin.

2. Kombination nach Anspruch 1, wobei das pharmazeutisch annehmbare Salz der Verbindung mit der Formel (I) das Natriumsalz ist.
3. Kombination nach Anspruch 1 zur Anwendung in der medizinischen Therapie.
4. Kombination nach Anspruch 1 zur Anwendung bei der Behandlung einer HIV-Infektion.
5. Pharmazeutische Zusammensetzung, umfassend eine Kombination nach Anspruch 1 zusammen mit einem pharmazeutisch annehmbaren Träger hierfür.
6. Kombination zur Anwendung nach Anspruch 4, wobei die Kombination gleichzeitig verabreicht wird.
7. Kombination zur Anwendung nach Anspruch 4, wobei die Kombination sequenziell verabreicht wird.
8. Verwendung einer Kombination nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung einer HIV-

Infektion.

Revendications

1. Combinaison comprenant un composé de formule (I)



ou un de ses sels pharmaceutiquement acceptables, et de la lamivudine.

2. Combinaison selon la revendication 1, dans laquelle le sel pharmaceutiquement acceptable d'un composé de formule (I) est le sel de sodium.
3. Combinaison selon la revendication 1 pour son utilisation dans une thérapie médicale.
4. Combinaison selon la revendication 1 pour son utilisation dans le traitement d'une infection au VIH.
5. Composition pharmaceutique comprenant une combinaison selon la revendication 1 conjointement avec un support pharmaceutiquement acceptable associé.
6. Combinaison pour son utilisation selon la revendication 4, dans laquelle la combinaison est administrée simultanément.
7. Combinaison pour son utilisation selon la revendication 4, dans laquelle la combinaison est administrée successivement.
8. Utilisation d'une combinaison selon la revendication 1 pour la fabrication d'un médicament destiné au traitement d'une infection au VIH.

REFERENCES CITED IN THE DESCRIPTION

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